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Abdominal organ motion during inhalation and exhalation breath-holds: pancreatic motion at different lung volumes compared

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Running head: Organ motion during different breath-holds

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Abstract

Purpose: Contrary to what is commonly assumed, organs continue to move during breath-holding.

We investigated the influence of lung volume on motion magnitude during breath-holding and changes in velocity over the duration of breath-holding.

Material and methods: Sixteen healthy subjects performed 60-second inhalation breath-holds in room-air, with lung volumes of ~100% and ~70% of the inspiratory capacity, and exhalation breath-holds, with lung volumes of ~30% and ~0% of the inspiratory capacity. During breath-holding, we obtained dynamic single-slice magnetic-resonance images with a time-resolution of 0.6 s. We used 2-dimensional image correlation to obtain the diaphragmatic and pancreatic velocity and displacement during breath-holding.

Results: Organ velocity was largest in the inferior-superior direction and was greatest during the first 10 s of breath-holding, with diaphragm velocities of 0.41 mm/s, 0.29 mm/s, 0.16 mm/s and 0.15 mm/s during BH_{100%}, BH_{70%}, BH_{30%} and BH_{0%}, respectively. Organ motion magnitudes were larger during inhalation breath-holds (diaphragm moved 9.8 and 9.0 mm during BH_{100%} and BH_{70%}, respectively) than during exhalation breath-holds (5.6 and 4.3 mm during BH_{30%} and BH_{0%}, respectively).

Conclusion: Using exhalation breath-holds rather than inhalation breath-holds and delaying irradiation until after the first 10 s of breath-holding may be advantageous for irradiation of abdominal tumors.

Introduction

Respiratory-induced motion of upper abdominal tumors during radiotherapy is often accounted for by using an internal target volume based on a pre-treatment 4-dimensional CT (4DCT), resulting in large treatment volumes and high dose values to surrounding healthy tissues [1]. However, several groups have shown that the respiratory motion of pancreatic tumors measured on a single pre-treatment 4DCT is not representative for daily tumor motion [2–4]. This discrepancy could limit the benefit of all 4DCT-based respiratory motion management techniques, such as using mid-ventilation [5].

Breath-holding can be used to reduce tumor motion during radiotherapy. Either inhalation or exhalation breath-holds are used in this technique, which is increasingly employed in many clinical applications in radiotherapy, including during irradiation of abdominal tumors [6–11]. Whether inhalation or exhalation breath-holding is used currently depends on the radiation technique and tumor type. For example, when using stereotactic body radiotherapy for pancreatic cancer, the planned dose to surrounding organs at risk was reduced when treatments were planned with the tumor at the exhalation rather than the inhalation position [12]. However, this was under the assumption that during breath-holding only minimal geometrical uncertainties remained.

The position variation of the tumor between multiple consecutive breath-holds, both inhalation and exhalation, has already been thoroughly determined for abdominal tumors [6,7,9,10,13,14]; mean variations of 1.2 and 2.3 mm were reported in the inferior-superior (IS) direction for inhalation and exhalation breath-holds, respectively [6,7]. The interfractional tumor position variation is similar for inhalation and exhalation breath-holds [15]. Preliminary results on abdominal tumor stability *during* exhalation breath-holds show good stability, but these studies also reported individual cases in which motion of up to 5 mm was observed during breath-holding [6,9]. Also, exhalation breath-holds are more challenging to perform and therefore often result in shorter breath-hold durations than inhalation breath-holds [6,9,16]. The generally good organ stability during exhalation breath-holds is

in great contrast with the large organ drifts that have been observed during inhalation breath-holds in healthy subjects and patients [13,14,17,18]. In addition, it was observed that the motion during inhalation breath-holds was more pronounced at the beginning of the breath-hold [17,18].

Even though both inhalation and exhalation breath-holds are being used for radiotherapy of abdominal cancer, the difference in organ motion during both breath-hold types has not previously been investigated [7,9,10,19]. However, to determine the optimal breath-holding procedure in terms of organ stability and feasibility, this difference must be known. Also, if the velocity of organ motion changes during breath-holding [17,18], the irradiation must be applied when the velocity is least.

In this study, we obtained magnetic resonance (MR) images at a high frequency during 60-second breath-holds with four different lung volumes in a group of 16 healthy subjects. We compared pancreatic and diaphragmatic motion magnitude and velocity during breath-holding between the different lung volumes. We determined which lung volume resulted in the most stable anatomy during breath-holding and whether the velocity changed during breath-holding.

Materials and methods

Subjects and measurement protocol

We studied 16 healthy subjects with a mean age of 32 years and no history of pulmonary disease (more characteristics in Supplementary Table E1). All subjects consented to participation in the study and abstained from eating and drinking in the two hours prior to the measurement. Each subject was instructed to perform twelve 60-second inhalation breath-holds; six with fully inflated lungs ($BH_{100\%}$) and six with a lung volume of $\sim 70\%$ of $BH_{100\%}$ ($BH_{70\%}$). In addition, each subject was instructed to perform twelve 60-second exhalation breath-holds; six with a lung volume of $\sim 30\%$ of $BH_{100\%}$ ($BH_{30\%}$) and six with fully deflated lungs ($BH_{0\%}$). All breath-holds were performed in room-air and the subjects did not receive any visual or mechanical guidance on their voluntary breath-holds. So, the lung volumes of 30% and 70% were based upon the subjects' perception and might differ between the three repeated breath-holds for each subject and lung volume. Simple audial instructions were given before the start of each breath-hold. The start of the breath-hold was defined when there was no more visible chest surface movement. Subjects were given a minute of free breathing between breath-holds. To avoid any order effect, half of the subjects performed the inhalation breath-holds prior to performing the exhalation breath-holds and the other half performed the breath-holds vice versa.

MRI measurement and motion acquisition

MR scans were obtained with an Ingenia 3T MR scanner (Philips Healthcare, Best, the Netherlands). During each breath-hold, we obtained images (one image every 0.6 s) using a fast single-slice steady-state free precession sequence (bandwidth = 538 Hz/voxel), resulting in 100 images per breath-hold. For each lung volume, we obtained coronal slices during the first three breath-holds and sagittal slices during the last three breath-holds. The slices (thickness, 8 mm; pixel size, $0.93 \times 0.93 \text{ mm}^2$) were positioned such that both the diaphragm and the pancreatic head were in the field of view.

Within each scan, the rigid pancreatic head and diaphragm displacements relative to the position at the start of breath-holding were obtained using a 2-dimensional image correlation algorithm, as used previously [13,20]. Displacements were determined by matching of a pre-determined template, containing the structure of interest (i.e. top of the right diaphragmatic dome or complete pancreatic head), to all images obtained during a single breath-hold. No deformable registration was used since only planar imaging was obtained and small organ displacements out of this plane could give a false representation of the organ deformation during breath-holding. To decrease the effects of small motion artifacts due to template mismatching, imaging artifacts or small organ deformations, we determined the pancreatic motion during breath-holding three times with different templates and averaged the results. Details about the algorithm can be found in the Supplementary Material.

Data analysis

We measured the motion magnitude of the pancreatic head over time in the IS and left-right (LR) direction (coronal scans) and in the IS and anterior-posterior (AP) direction (sagittal scans). The inferior, left and anterior directions were defined as the negative directions. In each direction, the motion magnitude of the pancreatic head during breath-holding was defined as the maximum difference in position in the respective direction within a single breath-hold. For the diaphragm, we only determined the motion magnitude in the IS direction. Before determining the motion magnitude, the motion data were smoothed using a moving average filter with a width of 5 data points to remove residual motion artifacts due to template mismatching and displacements due to cardiac motion.

We investigated whether it would be beneficial, in terms of organ stability, to delay irradiation of a patient for a certain amount of time after the start of breath-holding. To do so, we used a sliding time-frame of 20 s to determine the motion magnitude during 20 s of breath-holding, resulting in a simulated delay of 0 to 40 s. The differences in motion magnitude after a simulated delay of 0 s and

10 s were tested using the Wilcoxon signed-rank test. The cut off of 10 s was chosen to maintain potentially manageable breath-holding durations of 30 s.

To investigate the change in velocity during breath-holding, we calculated and compared the mean velocity of the pancreatic and diaphragmatic motion during the first 10 s of breath-holding and during the remainder of the breath-hold. The velocity was defined as the motion magnitude divided by the time over which it was measured. By using organ velocity, we excluded any effects of breath-hold duration (i.e. when there is a drift, longer breath-hold durations result in larger motion magnitudes). The differences in velocity were tested using the Wilcoxon signed-rank test.

In some cases the diaphragm is used as a surrogate for tumor motion while the patient is breathing freely [21]. We determined whether diaphragm motion can be used as a surrogate for pancreatic motion during breath-holding. This was done by determining the slope and strength of the linear association between the motion of the two structures. The unsmoothed motion of the pancreatic head and of the diaphragm during all breath-holds was plotted. For each breath-hold, a correlation plot of the motion of the pancreatic head in the IS or LR direction versus the motion of the diaphragm in the IS direction was created and their relation was analyzed by simple linear regression. In addition, we calculated the coefficient of determination (r^2) and distinguished between weak ($r^2 < 0.6$) and a strong ($0.6 \leq r^2 < 0.8$) to very strong linear associations ($r^2 \geq 0.8$). For the breath-holds for which we observed at least a strong association ($r^2 \geq 0.6$), we determined the mean slope of the linear fits, as this describes the relation between pancreatic and diaphragmatic motion.

The lateral location of the sagittal slice was based on the location of the pancreatic head, which resulted in a lateral location of the slice through the heart and the mediastinum. At this location, no accurate measurement of the diaphragm motion could be performed. Therefore, only the motion of the pancreatic head was obtained from the sagittal scans.

Results

60-second breath-holds were feasible for the majority of subjects (Fig. 1a), even exhalation breath-holds (BH_{30%} and BH_{0%}). The shortest performed breath-hold was with fully deflated lungs (BH_{0%}) and lasted 30.6 s.

Two typical examples of the diaphragm motion during the three repeated measurements during breath-holding with four different lung volumes are shown in Fig. 2. Substantial organ motion during the majority of breath-holds was observed in the coronal plane, but with considerable differences in motion magnitude between the different lung volumes. Furthermore, a clear change in velocity over time was observed. All results in this section were obtained from the coronal scans. Since the pancreatic motion data obtained from the sagittal scans could not be compared to the diaphragm motion, these data from the sagittal plane are shown only in the Supplementary Material.

For both the pancreatic head and diaphragm, the mean motion magnitude was larger during inhalation breath-holds (BH_{100%} and BH_{70%}) than during exhalation breath-holds (BH_{30%} and BH_{0%}) (Fig. 1b and c and Table 1). The differences in motion magnitude were not tested for significance because of different mean breath-hold durations for different lung volumes. The diaphragm motion during BH_{0%} of subject 2 could not be obtained because the diaphragm was outside the field of view.

Organ motion was more pronounced during the first 10 s of breath-holding compared with the remainder of the breath-hold. The mean motion magnitude over all volunteers of the pancreatic head during 20 s of BH_{100%}, BH_{70%} and BH_{30%} decreased significantly ($P < 0.001$) after a simulated delay of 10 s compared to a delay of 0 s (Fig. 3a). For the diaphragm, a significant ($P \leq 0.002$) decrease in mean motion magnitude for all four different lung volumes after a simulated delay of 10 s was observed (Table 1 and Fig. 3b).

The distributions and statistical significance of differences between the velocity of the pancreatic and diaphragmatic motion during the first 10 s of breath-holding and during the remainder of the breath-

hold are shown in Fig. 4; the group mean values can be found in Table 1. For each different lung volume, the velocity of both the pancreatic head and the diaphragm was significantly ($P \leq 0.002$) larger during the first 10 s compared to the remainder of the breath-hold. During the first 10 s of breath-holding, the pancreatic head and diaphragm velocity during inhalation breath-holds (BH_{100%} and BH_{70%}) was significantly larger than during exhalation breath-holds (BH_{30%} and BH_{0%}). During the remainder of the breath-hold, the differences in motion magnitudes between the different lung volumes were considerably smaller, and all four lung volumes appeared to result in a more stable anatomy after 10 s.

The group mean motion magnitude of the pancreatic head in the LR direction was 3.1 (SD: 1.3) mm, 2.9 (0.8) mm, 2.3 (0.5) mm and 2.9 (1.1) mm during BH_{100%}, BH_{70%}, BH_{30%} and BH_{0%}, respectively. In the LR direction, there were no significant differences in motion magnitude during breath-holding between the first 10 s and the remainder of the breath-hold for any of the four different lung volumes. All four group mean motion magnitudes of the pancreatic head in the LR direction during the first 20 s of breath-holding were ≤ 2.0 mm and decreased by ≤ 0.3 mm for a simulated delay of 10 s.

There was no clear relationship between the diaphragm motion and the motion of the pancreatic head during breath-holding. A strong or very strong linear association between the motion of the pancreatic head in the IS direction and the diaphragm motion in the IS direction was observed for only 82 out of the 192 analyzed breath-holds (Table 1). For the breath-holds with a (very) strong association, a large range in the slopes of the linear fits was observed (Table 1). Between the motion of the pancreatic head in the LR direction and of the diaphragm in the IS direction a (very) strong linear association for only 11 out of 192 breath-holds was observed (Table 1).

Discussion

With this study, we are the first to compare organ motion during breath-holding with different lung volumes within healthy subjects or patients. We showed that the motion magnitude in the IS direction was larger during inhalation breath-holds than during exhalation breath-holds and that the motion was more pronounced at the beginning of breath-holding. Delaying irradiation of a patient during the first 10 s of breath-holding may result in a considerably more stable anatomy during treatment. Due to the absence of a clear relation between pancreatic and diaphragmatic motion, the diaphragm cannot be used as a surrogate for pancreatic motion. Because we observed substantial motion of the diaphragm during breath-holding, it should be considered that all upper-abdominal organs may be affected by this motion.

Small deformations of the pancreatic head during breath-holding might interfere with accurate template matching. Possible motion artifacts have been minimized by averaging over three motion tracks, obtained using three different templates. To exclude any residual outliers and cardiac motion when determining the motion magnitude, the motion data was smoothed using a moving average filter. The unsmoothed data were used for the correlation plots because smoothed data would artificially increase r^2 . The effect of deformations, which are small and random in nature, on dose distributions is negligible [22,23].

The position variation between consecutive breath-holds may be highly dependent on the used breath-holding procedure. For example, using a spirometer to measure airflow or using an active breathing control system, as is typically done in the clinic, might result in more reproducible tumor positions. We did not have such systems available for our MRI measurements, which may have resulted in differences in lung volume when performing three repeated measurements of the same breath-hold type within a single subject. Therefore, we did not include position variation between consecutive breath-holds in our analyses. The voluntary breath-holds used in this study (i.e. without

mechanical guidance) can be used in patients as well, but note that the tumor position variation between breath-holds must be accounted for in daily practice.

Visual determination of the start of breath-holding may not be as accurate as using an active breathing control system. However, it is unlikely that the transition from free-breathing to breath-holding would explain the typical motion observed in the first 10–20 s of breath-holding as shown in Fig. 2. In addition, the observation that organ motion is more pronounced during the start of breath-holding is also reflected in the data from earlier studies [18,24]. They reported a mean diaphragm velocity of 1.58 mm/s during the first 3.64 s of inhalation breath-holding compared with a mean velocity of 0.27 mm/s during the remainder of the 20-second breath-hold [18]. Parkes *et al.* reported some settlement of the chest surface during the first 15 s of breath-holding [24]. So, delaying treatment for a certain amount of time after the start of breath-holding can result in a more stable anatomy. However, the required delay varies for individual subjects and the optimal delay for specific patient groups needs to be determined. In addition, delaying irradiation may result in a more stable anatomy during irradiation, but would also require longer breath-hold durations or result in shorter irradiation times per breath-hold. The change in velocity complicates daily patient positioning because the organ position variations between consecutive breath-holds after an introduced delay should also be determined if this approach is to be implemented in radiotherapy. In addition, the observed motion velocities might substantially decrease the treatment accuracy, and the resulting tumor displacement must be accounted for.

Exhalation breath-holds, especially BH_{0%}, can be challenging for patients, but have been shown to be feasible [6,8–10]. Berson *et al.* included 108 patients with different tumor types who were able to perform multiple short (7–15 s) exhalation breath-holds during treatment [8]. However, it would not be possible to combine these short breath-holds with a possible delay after the start of breath-holding. For liver cancer patients, similar exhalation breath-hold durations were achieved [6,9]. Nakamura *et al.* showed that 9 out of 10 included pancreatic cancer patients were able to perform

30-second exhalation breath-holds and all patients were able to perform 20-second breath-holds [10]. All four studies used voluntary breath-holding with room-air at lung volumes that could best be compared to the BH_{30%} that was used in this study. Even though breath-holding durations of one minute may prove to be too difficult for patients, the expected benefit of exhalation breath-holds will also hold for shorter breath-holding durations. However, a delay after the start of breath-holding may not be feasible for the patient or the effective treatment time after such a delay may be insufficient for treatment delivery. For patients who are only able to perform relatively short breath-holds, the benefit of breath-holding compared with other motion management strategies should be determined while taking into account the position variation between multiple breath-holds, patient feasibility and treatment time.

Earlier, we performed a patient study in which we determined the tumor motion during 30-second inhalation breath-holds with a lung volume of ~75% of the inspiratory capacity (lung volumes were determined using a spirometer) [13,14]. When comparing our current data to the patient data from that study, we see that the observed tumor motion magnitude in the IS direction during 30-second inhalation breath-holds in patients (mean: 4.7 mm; SD: 3.0 mm) was similar to the motion of the pancreatic head in the IS direction during the first 30 s of BH_{70%} in this study (mean: 4.8 mm; SD: 2.3 mm). In both studies, we observed motion predominantly in the form of drifts in the superior direction. These organ drifts can be explained by the decreasing lung volume during breath-holding due to the continuous uptake of oxygen without replenishment of CO₂ [16,25,26]. In both the patient study and the current study there was no clear relation between the motion of the diaphragm and the motion of the pancreas (i.e. pancreatic head or tumor). The change in tumor and diaphragm velocity during breath-holding was not determined for the patients. A future study should be performed using visually guided breath-holds with different lung volumes in patients to determine which breath-hold yields the least tumor motion during breath-holding. Such a study could be used to determine differences in tumor position variation between breath-holds as well as to ensure that the transition period between free-breathing and breath-holding is excluded.

To improve breath-holding procedures, exhalation breath-holds (i.e. BH_{30%} and BH_{0%}) may be used and treatment delivery may be delayed after the patient starts breath-holding. Of these two different exhalation breath-holds, BH_{30%} is potentially the most suitable as this lung volume proved to be easily achievable by the included subjects. Delaying irradiation should be combined with intratumoral fiducials and daily cone-beam CTs to correct for interfractional tumor position variations [27–29]. As breath-holds are being used to stabilize abdominal tumors, the procedures should be optimized further in order to minimize the effects of decreasing lung volume and consequential tumor drifts during breath-holding. Introducing training for patients to extend breath-holding durations is beneficial [30]. As is the use of an active breathing control system [31]. Extended breath-hold durations may be helpful as this would simplify the introduction of an irradiation delay. Especially since this delay is only feasible for patients who can perform breath-holds of sufficient duration (i.e. at least 20–30 s). Breath-hold durations of >5 minutes have been shown to be feasible [24,30]. It may also be considered to use breath-holding in combination with a MR-guided linear accelerator system that can visualize tumor motion during irradiation [32,33]. Tracking of the tumor might be easier for slow tumor drifts during breath-holding than for tumor motion during free breathing.

In conclusion, considerable motion magnitudes of the pancreatic head and diaphragm during the majority of breath-holds were observed regardless of lung volume, but motion magnitudes were larger during inhalation breath-holds (BH_{100%} and BH_{70%}) than during exhalation breath-holds (BH_{30%} and BH_{0%}). Organ velocity was significantly greater during the first 10 s of breath-holding than during the remainder of the breath-hold. Delaying irradiation of patients with intra-abdominal cancer after the start of breath-holding may result in a more stable anatomy during treatment for both inhalation and exhalation breath-holding. Furthermore, diaphragm motion cannot be used as a surrogate for pancreatic motion.

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Table 1: Measurements obtained from the coronal breath-hold scans for different lung volumes

	BH _{100%} [*]	BH _{70%}	BH _{30%}	BH _{0%}
Number of subjects	16	16	16	16
Number of breath-holds	48	48	48	48
Pancreatic motion in IS during breath-holding				
- Group mean magnitude (mm) [†]	7.0	6.5	4.4	4.2
- Group SD (mm)	4.3	2.8	1.6	1.8
Diaphragmatic motion in IS during breath-holding				
- Group mean magnitude (mm)	9.8	9.0	5.6	4.3
- Group SD (mm)	5.9	5.0	2.2	2.1
Decrease in group mean motion magnitude for a simulated delay of 10 s [‡]				
- Pancreatic (mm)	1.4	1.3	0.6	0.3
- Diaphragmatic (mm)	3.2	2.0	0.8	0.5
Group mean pancreatic velocity in IS				
- During first 10 s (mm/s)	0.34	0.27	0.18	0.20
- During remainder (mm/s)	0.09	0.08	0.06	0.09
Group mean diaphragmatic velocity in IS				
- During first 10 s (mm/s)	0.41	0.29	0.16	0.15
- During remainder (mm/s)	0.10	0.11	0.08	0.09
# of linear associations (out of 48 breath-holds) between pancreatic and diaphragmatic motion in IS				
- Strong ($0.6 \leq r^2 < 0.8$)	8	11	14	6
- Very strong ($r^2 \geq 0.8$)	18	22	3	0
Linear fit slope for $r^2 \geq 0.6$ between pancreatic and diaphragmatic motion in IS				
- Mean slope (mm/mm)	0.73	0.65	0.72	0.96
- Range (mm/mm)	0.26–1.26	0.34–1.36	0.37–1.05	0.47–1.74
# of linear associations between pancreatic motion in LR and diaphragmatic motion in IS				
- Strong ($0.6 \leq r^2 < 0.8$)	3	4	2	1
- Very strong ($r^2 \geq 0.8$)	0	1	0	0

Abbreviations: IS = inferior-superior; SD = standard deviation; LR = left-right.

^{*}BH_{xxx%} represents a breath-hold with a lung volume of xxx% of the inspiratory capacity

[†]For all group mean values we first determined the mean per volunteer and the average of these means is the group mean value.

[‡]Group mean motion magnitude during the first 20 s of breath-holding minus group mean motion magnitude for a delay of 10 s (i.e. during time frame 10–30 s).

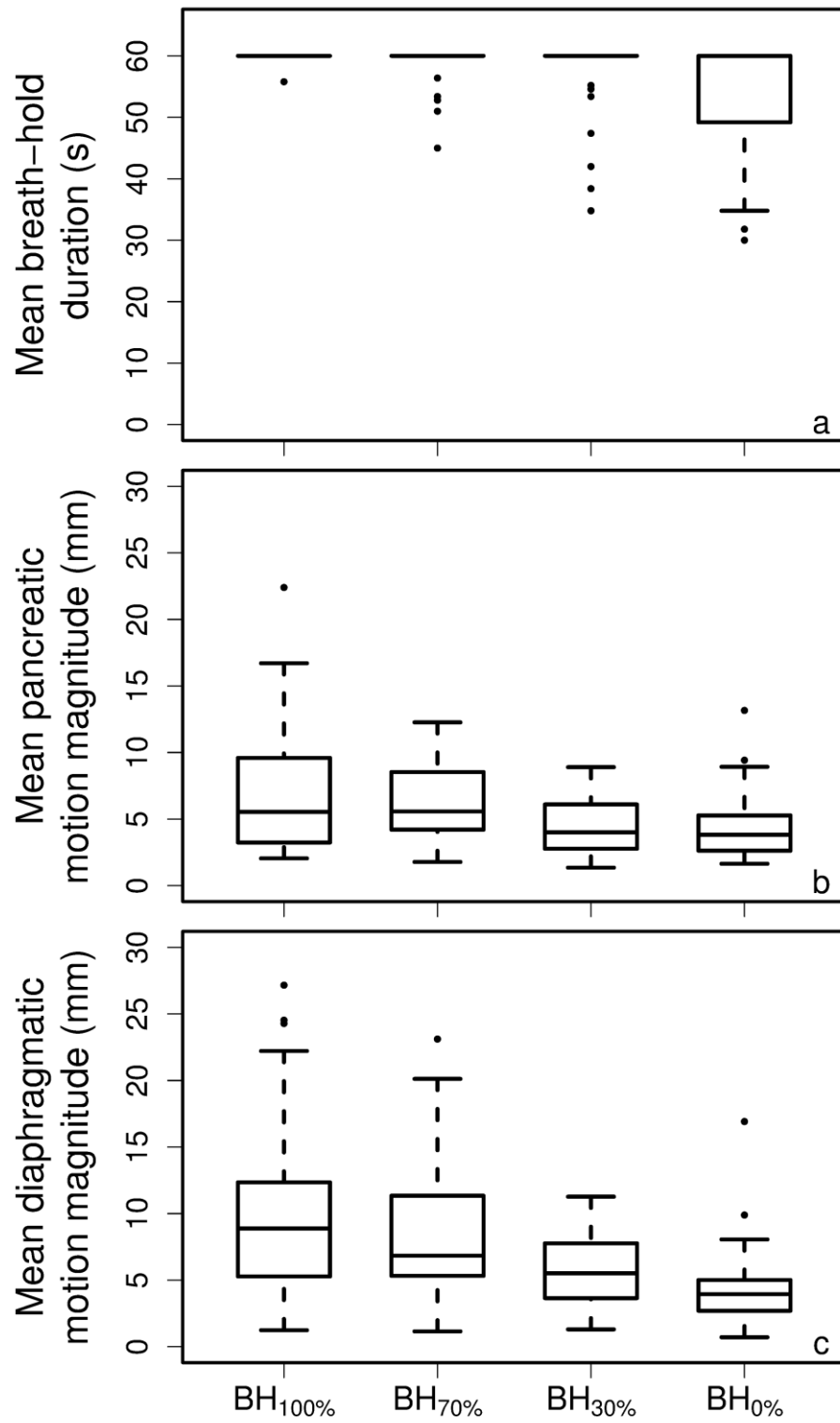


Figure 1: Mean breath-hold durations (a) and mean pancreatic (b) and diaphragmatic (c) motion magnitudes in the inferior-superior direction during breath-holding with four different lung volumes in all subjects (48 breath-holds per box). Boxes: median value and upper and lower quartiles; whiskers: lowest and highest data point within $1.5 \times$ inter-quartile range; dots: outliers.

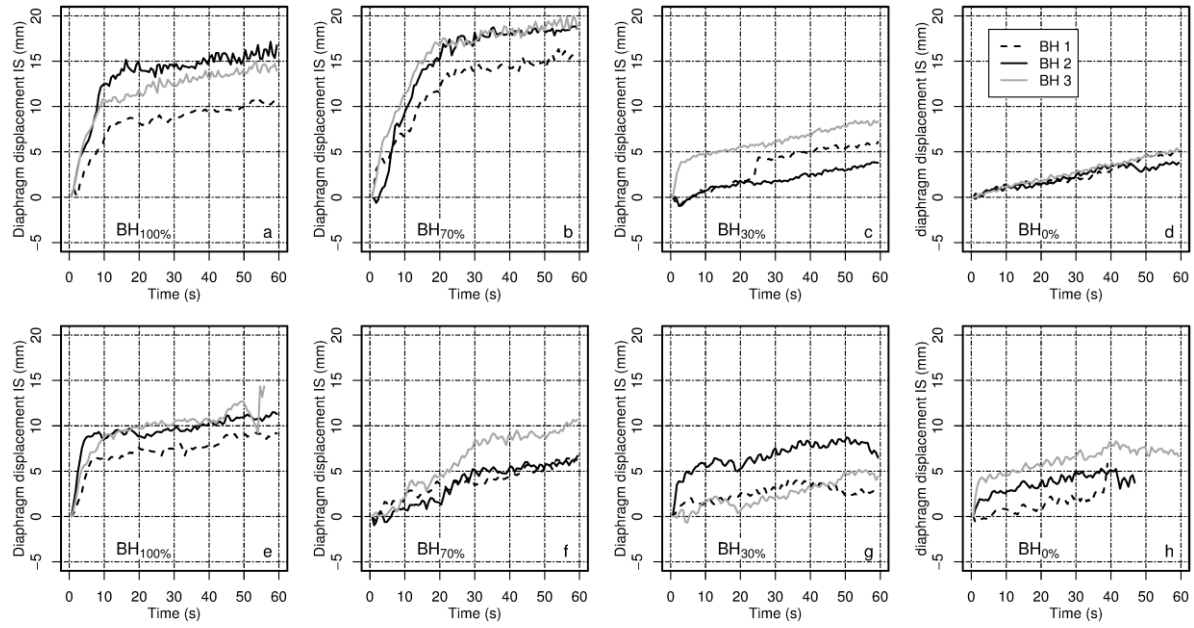


Figure 2: Two typical examples (subject 3, a–d; subject 12, e–h) of diaphragm motion in the inferior-superior (IS) direction during the three measurements of the four breath-holds with different lung volumes, showing the predominance of the motion during the first 10 s. BH_{100%} and BH_{0%} of subject 12 (e and h) had a variable duration due to inability of the subject to maintain the 60-second breath-holds.

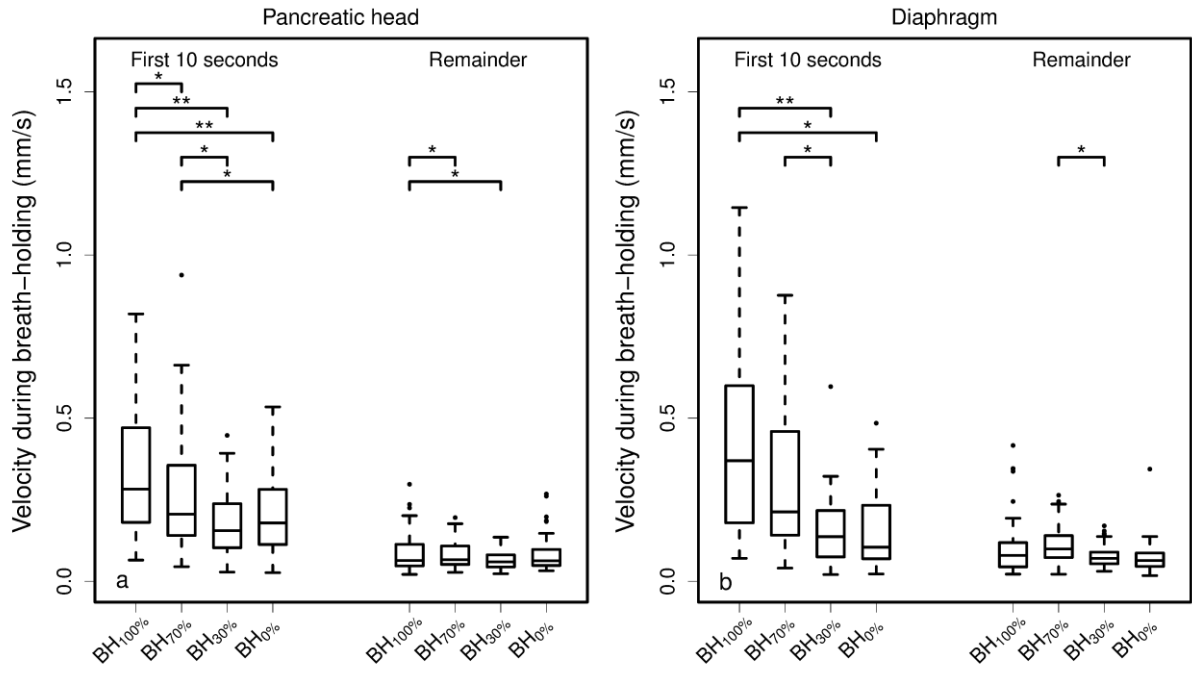


Figure 3: Mean motion magnitude in the inferior-superior direction over the 16 subjects during 20 s of breath-holding with different lung volumes, for pancreatic head (a) and diaphragm (b) after a simulated delay, as obtained from the coronal MR scans. When ≥ 5 out of 48 breath-holds ($\sim 10\%$) were not available, because the delay plus 20 s exceeded the total duration of those breath-holds, open symbols were used.

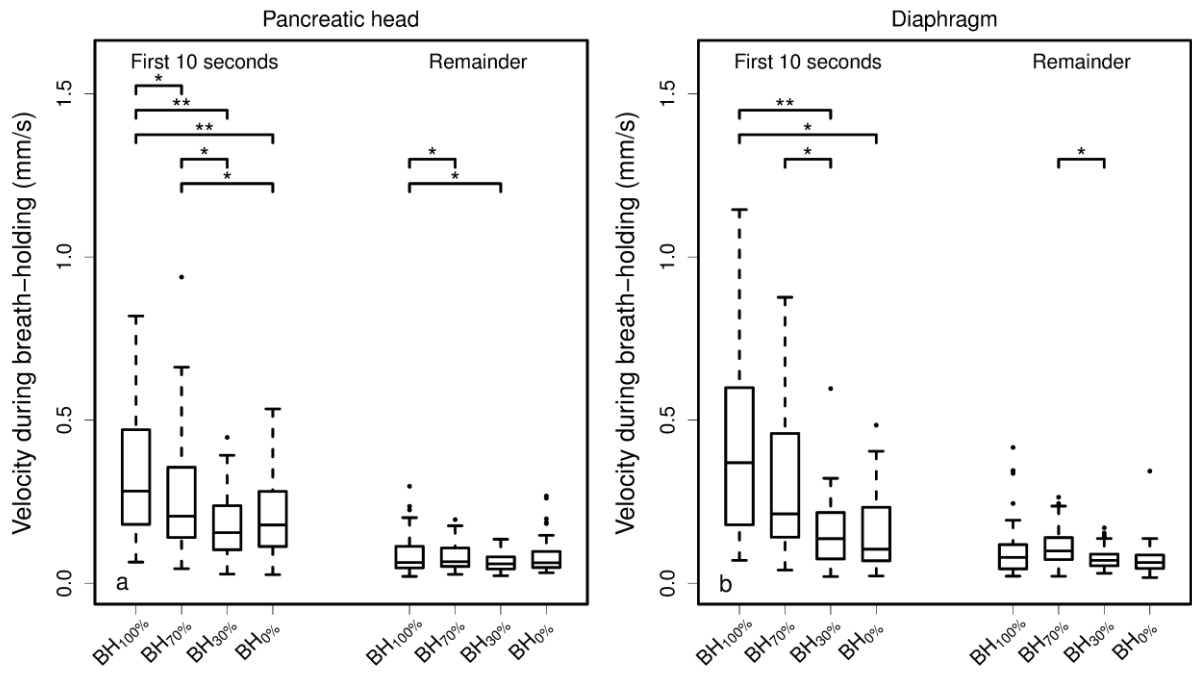


Figure 4: Boxplots of the pancreatic head (a) and diaphragm (b) velocity in the inferior-superior direction during the first 10 seconds of breath-holding and during the remainder of the breath-hold, for the four different lung volumes (48 breath-holds per lung volume), as obtained from the coronal MR scans. Significant differences are indicated by * ($0.01 < P \leq 0.05$) and ** ($0.001 < P \leq 0.01$).

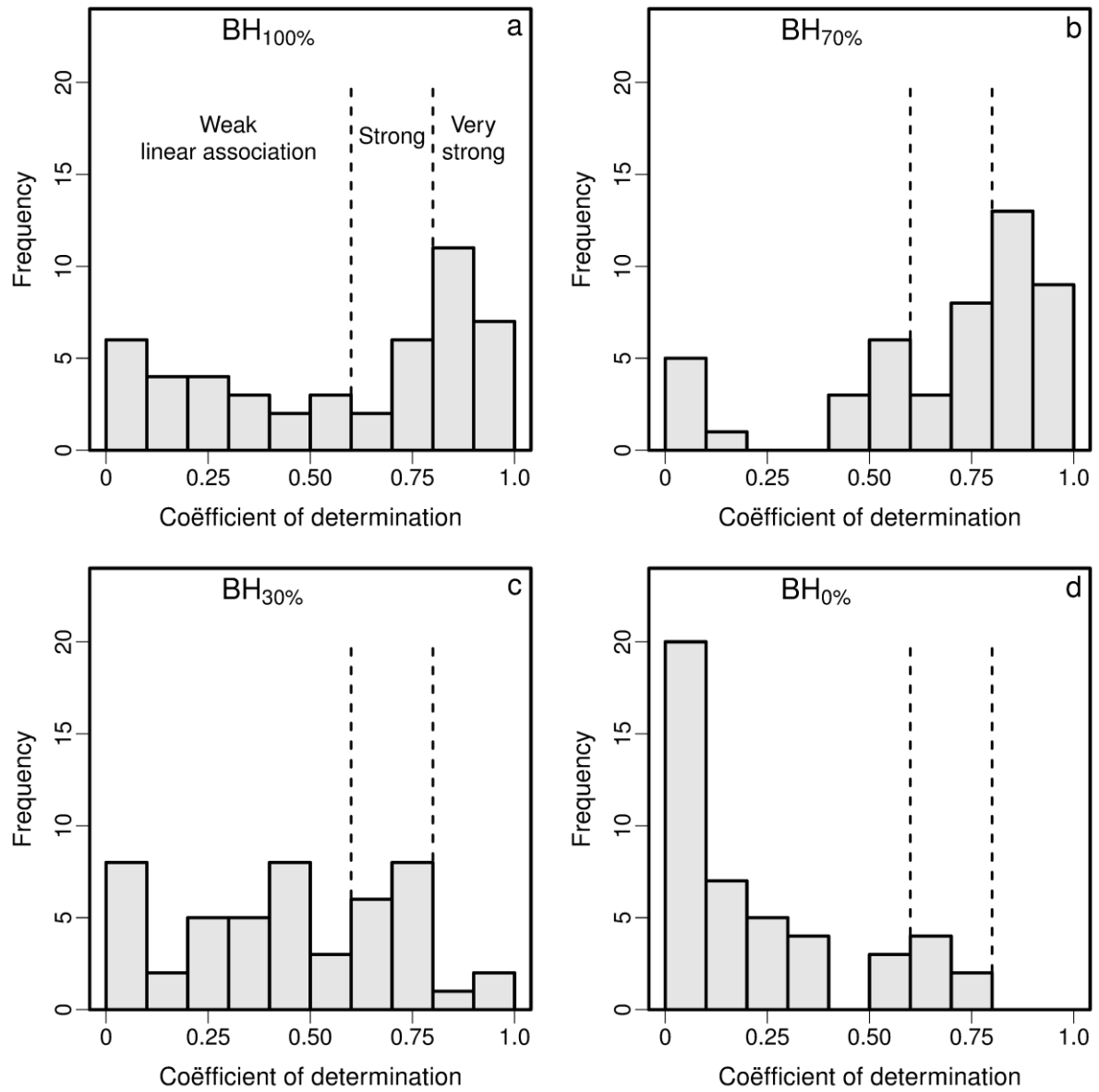


Figure 5: Histograms of the coefficients of determination (r^2) between the motion of the pancreatic head and of the diaphragm in the inferior-superior direction during the breath-holds with four different lung volumes, as obtained from the coronal MR scans.